Short and Stereoselective Synthesis of (±)-Ibogamine via a Vinylsulfone Intermediate, IV[1a]

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Ibogamine (**11b**) was synthesized starting from the vinyl sulfone **3**. Addition of organocuprate reagents to **3** furnished **2a–d** with high stereoselectivity. Only products from the *syn* addition of the cuprate reagents could be detected. Functional group transformations provided **7a,b** the key intermediates for the synthesis of (±)-21-noribogamine (**11a**) and (±)-ibogamine (**11b**).

Since the structure determination of ibogamine (**11b**) by Taylor[2] and since its first synthesis by Büchi and co-workers[3] this compound has been the subject of extensive synthetic investigations[3,4]. Also catharanthine (18-methoxycarbonyl-Δ^3-**11b**) as a synthetic precursor of anhydrovinblastine and vinblastine has attracted the interest in the synthesis of this class of compounds[3c,4i,j,k,l]. Two different strategies for the construction of the isoquinuclidine ring system have been elaborated, the Diels-Alder additions to dihydropyridines[3,4i,j,k,l] or 2-pyridones[4f] and the bridging of 4-substituted cyclohexenes[4a,b,c,g].

The 2-pyridone approach has shown major disadvantages in the regio- and stereochemistry of the cycloaddition of methyl acrylate to 1-benzyl-2-pyridone due to the structure of the diene moiety[4f]. Therefore, we have envisaged 1-benzyl-5-benzyloxy-2(1*H*)-pyridone (**1**) as starting material for two reasons. First, it behaves like an electron-rich diene in the cycloaddition reaction with acceptor-substituted olefins[1]; second, the resulting benzyl enol ether in the product can easily be transformed into a keto group in the correct position for ring closure with the indole moiety.

We have previously shown that **3** can be synthesized in gram amounts via [4 + 2] cycloaddition of (*E*)-1,2-bis(phenylsulfonyl)ethene to **1**[1b]. The key step of the overall reaction sequence is the stereocontrolled *syn* addition of nucleophiles to the vinyl sulfone **3**[1b]. We found that organocuprates add with high *syn* diastereoselectivity to the bicyclic vinyl sulfone[5] **3** to produce the *trans* adducts **2a–d** (Path A). Only in the case of **2b** a small amount of the *cis* adduct has been isolated (see Table 1 entry 7). The assignment of the *syn* configuration of the substituent R (**2a–d**) has unambiguously been made on the basis of the ^{1}H-NMR spectra (Table 2; see also Table 1 in ref.[1b]). Characteristically $J_{1,8\text{-}anti}$ is observed in the range of 1.0–2.1 Hz and $J_{1,6\text{-}syn}$ = 2.4–4.2 Hz[1b]. The high stereoselectivity of this *syn* addition can be easily understood in terms of a large unfavorable 1,3-diaxial interaction between an *anti*-entering nucleophile and one of the methoxy substituents of the acetal function. This argument corresponds well with the observation that lithium dimethylcuprate addition to the ketone derivative of **3** provides only a product resulting from the *anti* attack of the carbon nucleophile to the vinyl sulfone moiety[6].

Scheme 1

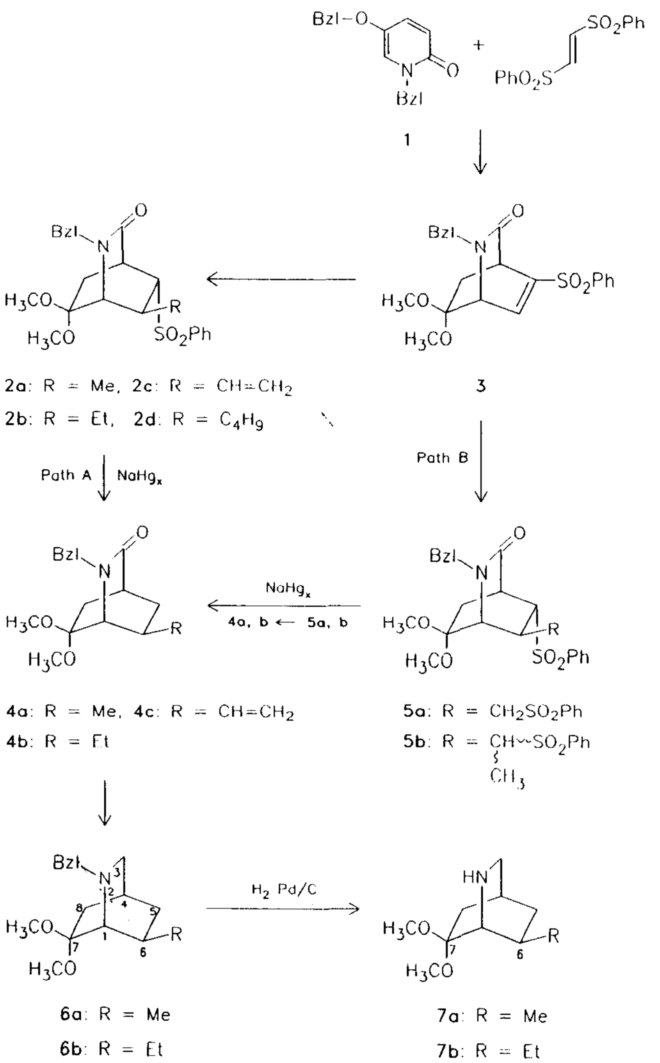

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Table 1. Reaction of **3** with organometallic reagents

Entry	Nucleophile	Equiv. of Organomet. reag.	Solvent	Temp. [°C]	Time [h]	Isolated yield (%)	Compound No
1	MeLi	1.0	THF	−78	1	36	**2a**
2	MeMgI	3.0	THF	−78	3	0[d]	–
3	MeMgI	3.0	THF	+20	12	45	**2a**
4	Me_2CuLi	5.0	Et_2O	−78	2	0	–
5	Me_2CuLi[a]	5.0	Et_2O	−20	2	98	**2a**
6	Me_2CuMgI[a]	5.0	Et_2O	0	2	81	**2a**
7	Et_2CuMgI[a]	5.0	Et_2O	−20	2	97[b]	**2b**[a]
8	$(H_2C{=}CH)_2CuMgBr$[a]	5.0	Et_2O	−20	1.5	77	**2c**
9	$(H_2C{=}CH)_2CuMgBr$[a]	2.5	Et_2O	−20	3	0[d]	–
10	$(H_2C{=}CH)_2CuMgBr$[a]	2.5	Et_2O	+20	3	0[d]	–
11	$(n\text{-}Bu)_2CuLi$[a]	5.0	Et_2O	−20	2	92	**2d**
12	$PhSO_2CH_2Li$	1.1	THF	−78 to +20	0.5	77	**5a**[c]
13	$PhSO_2(CH_3)CHLi$	1.1	THF	−78 to +20	0.5–18	86	**5b**[c]

[a] CuBr–Me_2S as copper source. — [b] 81% *trans* and 16% *cis*. — [c] See ref.[1h]. — [d] Starting material was recovered unchanged.

In Table 1 are listed representative results of our investigations on the introduction of a carbon substituent via organocuprate addition to the vinyl sulfone **3**[7]. Three conditions for achieving optimum results are noteworthy: (i) the reaction temperature has to be in the range from −20°C to 0°C, (ii) five equivalents of organocuprate reagent must be used (entries 8,9) and (iii) other copper sources than CuBr–Me_2S (cf. CuI, CuCN) give poor yields of the addition product.

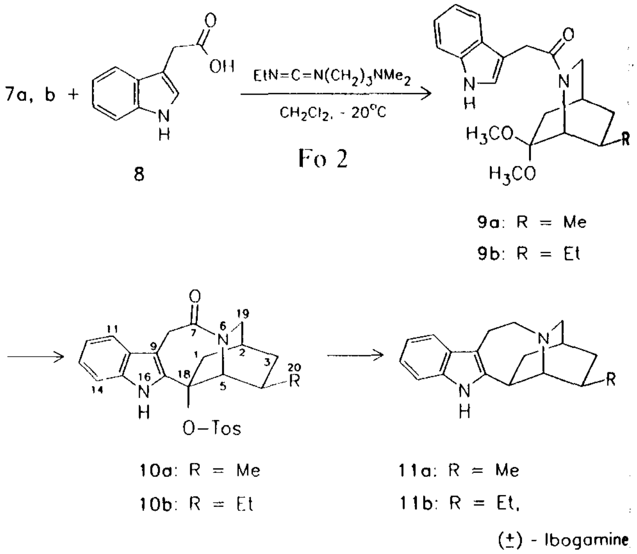
Table 2. ^{1}H-NMR $J_{1,6}$ coupling constants

Compound No	$J_{1,6\text{-}anti}$[a]
2a	1.0
2b (*trans*)	1.1
2b (*cis*)	1.0
2c	1.1
2d	1.0
5a	1.0
5b	1.5

[a] For $J_{1,6\text{-}syn}$ coupling values see ref.[1h].

We have been surprised to find that also α-sulfonyl carbanions (entries 12,13) add in high yields and exclusively with *syn* stereoselectivity[1h] (Path B). This is an efficient alternative approach to **4a,b** after reductive desulfonylation of **5a,b** with 6% sodium amalgam[9]. Treatment of **2a–e** in the same way (buffered methanol, 10-fold excess of sodium amalgam) provides **4a–e** in excellent yields. Reduction of **4a,b** with lithium tetrahydridoaluminate furnishes **6a,b** which, on catalytic hydrogenation with palladium on carbon in methanol, are converted into **7a,b** as oils. These oils are sensitive to light and oxygen. Starting from **1**, **7a** and **7b** can be prepared in 8 steps via path A in an overall yield of 82% and 76%, respectively. Path B provides **7a,b** in the lower yields of 60% and 65%, respectively.

Scheme 2



Treatment of **7a** and **7b** with 3-indolylacetic acid (**8**) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[10,3c] in dichloromethane at −20°C affords crystalline **9a,b**. In contrast, Hanaoka et al.[4c] have found **9b** as a colorless oil. Cyclization of **9a,b** with 2 equivalents of anhydrous *p*-toluenesulfonic acid[4d,4c] affords **10a,b**. Reduction of **10a,b** with $LiAlH_4/AlCl_3$[11,4e] proceeds cleanly in THF to provide (±)-noribogamine (**11a**) and (±)-ibogamine (**11b**) in 22% and 14% overall yield from **1** in 11 steps.

Analytical data, especially ^{13}C-NMR data of **11b** are in complete accordance with literature values[11].

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Experimental

IR: Perkin-Elmer 681. — ^{1}H-NMR (TMS as internal standard): Bruker AC 200 (200 MHz), Jeol GX 400 (400 MHz). — ^{13}C-NMR:

Bruker AC 200 (200 MHz). – MS: Varian CH 7 (70 eV), high-resolution MS: Vacuum Generators 70/70 (70 eV). – Melting points (uncorrected values): Büchi 510. – TLC: Merck silica gel 60 GF_{254}, 0.25 mm, UV detection or/and iodine vapor. – Column chromatography: Merck silica gel 60 (0.063–0.2 mm) or neutral Al_2O_3 90. – Purification of solvents and chemicals see ref.[12]. All organometallic reactions were conducted under purified, dried and oxygen-free (R3-11 catalyst, BASF) nitrogen.

Preparation of the Starting Materials: 1-Benzyl-5-benzyloxy-2-(1*H*)-pyridone (**1**) was prepared as reported previously[8] from 5-Hydroxy-2(1*H*)-pyridone[13] (8.88 g, 80 mmol); yield 17.3 g (74%) of **1**. Freshly prepared 5-hydroxy-2(1*H*)-pyridone should be used and the reaction should be conducted under nitrogen. – (*E*)-1,2-Bis-(phenylsulfonyl)ethene was prepared in the same manner as reported previously[14]. – (±)-2-Benzyl-7,7-dimethoxy-5-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-5-en-3-one (**3**) and (±)-(5-*anti*,6-*syn*)-2-benzyl-7,7-dimethoxy-5-(phenylsulfonyl)-6-[1-(phenylsulfonyl)-ethyl] 2-azabicyclo[2.2.2]octan-3-one (**5b**) were prepared as described in ref.[1b].

(±)-(5-anti,6-syn)-2-Benzyl-7,7-dimethoxy-6-methyl-5-(phenylsulfonyl)-2-azabicyclo[2.2.2]octan-3-one (**2a**): Copper(I) bromide–dimethyl sulfide complex (2.57 g, 12.50 mmol) was suspended in dry ether (100 ml) and methyllithium (15.5 ml, 25.0 mmol, 1.6 M in ether) was added at –20°C with stirring. To this solution **3**[1b] (1.034 g, 2.50 mmol) was added, and the yellow suspension was stirred at –20°C for 2 h. After the addition of satd. ammonium chloride solution the mixture was extracted with dichloromethane (4×). The combined organic extracts were washed with water, dried (Na_2SO_4), and the solvent was evaporated to give a colorless oil which solidified upon trituration with ether; yield 1.05 g (98%) colorless crystals, m.p. 204–205°C. – IR (KBr): $\tilde{\nu}$ = 1662 cm^{-1} (C=O), 1451, 1305, 1150, 1131, 1045. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.48 (d, J = 6.8 Hz, 3H, CH_3), 1.75 (dd, $J_{4,8}$ = 3.8 Hz, $J_{8a,8s}$ = 15.8 Hz, 1H, 8-H_s), 2.83 (m, 4H, 4-, 5-, 6-H, 8-H_a), 3.08 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 3.39 (d, J = 1.0 Hz, 1-H), 3.92 (d, J_{AB} = 14.3 Hz, 1H, NCH), 5.02 (d, J_{AB} = 14.3 Hz, 1H, NCH), 7.24–7.68 (m, 10H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 19.1 (CH_3), 28.4/29.0 (C-6, -8). 40.0 (C-4), 48.2 (NCH_2), 49.4 (OCH_3), 49.7 (OCH_3), 62.5 (C-5), 66.1 (C-1), 103.3 (C-7), 127.9, 128.4, 129.5, 134.1, 123.3 ($C_{arom.}$), 170.7 (C-3).

$C_{23}H_{27}NO_5S$ (429.5)
Calcd. C 64.32 H 6.34 N 3.26
Found C 64.67 H 6.63 N 3.30

(±)-(5-anti,6-syn)-2-Benzyl-6-ethyl-7,7-dimethoxy-5-(phenylsulfonyl)-2-azabicyclo[2.2.2]octan-3-one (**2b**) *and Its (±)-(5-syn,6-syn)-Diastereomer:* Prepared in the same manner as described above, but with ethyllithium instead of methyllithium. The colorless powder was dissolved in hot ethanol and filtered. After cooling colorless needles of **2b** separated. Flash chromatography of the mother liquor ($CHCl_3$/ethyl acetate, 9 + 1) provided another crop of **2b** and its *syn,syn* diastereomer.

2b: Yield 0.90 g (81%), m.p. 186°C (EtOH). – IR (KBr): $\tilde{\nu}$ = 1656 cm^{-1} (C=O), 1148, 1125, 1082, 1055. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.36 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.61 (m, 1H, CH_2CH_3), 1.12 (m, 1 h, CH_2CH_3), 1.82 (ddd, $J_{5,8e}$ = 1.7 Hz, $J_{4,8}$ = 3.7 Hz, $J_{8a,8s}$ = 14.8 Hz, 1H,8-H_s), 2.56 (m, 1H, 6-H), 2.79 (m, 3H, 4-, 5-H, 8-H_a). 3.14 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.60 (d, $J_{1,6}$ = 1.1 Hz, 1H, 1-H), 3.85 (d, J_{AB} = 14.2 Hz, 1H, NCH), 5.12 (d, J_{AB} = 14.2 Hz, 1H, NCH), 7.25–7.88 (m, 10H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 11.0 (CH_2CH_3), 25.9 (CH_2CH_3), 28.9 (C-8), 35.9 (C-6), 40.2 (C-4), 48.2 (OCH_3), 49.2 (OCH_3), 49.7 (NCH_2), 57.8 (C-5), 65.4 (C-1), 103.5 (C-), 128.0, 128.4, 128.6, 129.5, 129.7, 134.1, 136.6, 138.5 ($C_{arom.}$), 171.0 (C-3).

$C_{24}H_{29}NO_5S$ (443.6)
Calcd. C 64.99 H 6.59 N 3.16
Found C 64.80 H 6.46 N 3.27

5-syn,6-syn Diastereomer: Yield 0.18 g (16%) colorless cubes, m.p. 185°C (EtOH). – IR (KBr): $\tilde{\nu}$ = 1678 cm^{-1} (C=O), 1455, 1445, 1325, 1310, 1158, 1132. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.39 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.33 (m, 1H, CH_2H_3), 1.50 (dd, $J_{4,8a}$ = 2.5 Hz, $J_{8a,8s}$ = 14.2 Hz, 1H, 8-H_a), 2.01 (dd, $J_{4,8s}$ = 3.8 Hz, $J_{8a,8s}$ = 14.2 Hz, 1H, 8-H_s), 2.33 (m, CH_2CH_3, 1H), 2.48 (m, 2H, 4-, 6-H), 3.07 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.45 (dd, $J_{4,5}$ = 1.7 Hz, $J_{5,6}$ = 10.4 Hz, 1H, 5-H), 3.61 (d, $J_{1,6}$ = 1.0 Hz, 1H, 1-H), 3.99 (d, J_{AB} = 14.3 Hz, 1H, NCH), 5.22 (d, J_{AB} = 14.3 Hz, 1H, NCH), 7.29–8.05 (m, 10H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_2CH_3), 18.8. (CH_2CH_3), 35.4 (C-8), 38.5 (C-6), 40.8 (C-4), 48.1 (NCH_2), 48.9 (OCH_3), 49.8 (OCH_3), 57.4 (C-5), 64.5 (C-1), 103.5 (C-7), 127.7, 128.4, 129.2, 129.3, 129.9, 133.7, 136.5, 138.9 ($C_{arom.}$), 170.1 (C-3).

$C_{24}H_{29}NO_5S$ (443.6)
Calcd. C 64.99 H 6.59 N 3.16
Found C 64.74 H 6.40 N 3.00

(±)-(5-anti,6-syn)-2-Benzyl-7,7-dimethoxy-5-(phenylsulfonyl)-6-vinyl-2-azabicyclo[2.2.2]octan-3-one (**2c**): Prepared in the same manner as described above with copper(I) bromide–dimethyl sulfide complex (0.514 g, 2.5 mmol) in dry ether (30 ml) and vinylmagnesium bromide solution (5.0 ml, 5 mmol, 1 M in THF). To this green-black solution **3** (0.2 g, 0.5 mmol) was added. After workup as above the residue was recrystallized from ethanol; yield 0.17 g (77%) light yellow needles, m.p. 185–186°C (EtOH). – IR (KBr): $\tilde{\nu}$ = 1660 cm^{-1} (C=O), 1450, 1305, 1295, 1120, 1132. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.81 (ddd, $J_{5,8s}$ = 1.5 Hz, $J_{4,8s}$ = 3.2 Hz, $J_{8a,8s}$ = 14.4 Hz, 1H, 8-H_s), 2.86 (dd, $J_{4,8a}$ = 2.0 Hz, $J_{8a,8s}$ = 14.4 Hz, 1H, 8-H_a), 3.00 (s, 3H, OCH_3), 3.12 (m, 2H, 4-, 6-H), 3.28 (m, 1H, 5-H), 3.49 (d, $J_{1,6}$ = 1.1 Hz, 1H, 1-H), 4.03 (d, J_{AB} = 14.4 Hz, 1H, NCH), 4.52–4.85 (m, 3H, $CH=CH_2$), 4.87 (d, J_{AB} = 14.4 Hz, 1H, NCH), 7.25–7.85 (m, 10H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 29.0 (C-8), 38.9 (C-6), 39.9 (C-4), 48.1 (OCH_3), 49.9 (NCH_2), 62.6 (C-5), 63.8 (C-1), 102.9 (C-7), 117.2 ($CH=CH_2$), 127.8, 128.5, 129.4, 129.5, 134.0, 136.3, 138.6 ($C_{arom.}$), 136.5 ($CH=CH_2$), 170.8 (C-3).

$C_{24}H_{27}NO_5S$ (441.5)
Calcd. C 65.29 H 6.16 N 3.17
Gef. C 65.38 H 6.06 N 3.25

(±)-(5-anti,6-syn)-2-Benzyl-6-butyl-7,7-dimethoxy-5-(phenylsulfonyl)-2-azabicyclo[2.2.2]octan-3-one (**2d**): Prepared in the same manner as described for **2a** copper(I) bromide–dimethyl sulfide complex (1.028 g, 5 mmol) in dry ether (60 ml) and butyllithium (6.3 ml, 10 mmol, 1.6 M in *n*-hexane). To this solution **3** (0.41 g, 1.0 mmol) was added. After workup the green oil was chromatographed on neutral Al_2O_3 with $CHCl_3$/*n*-hexane (9 + 1). The oily residue was triturated with ether; yield = 0.42 g (92%) colorless crystals, m.p. 175°C. – IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1}, 1663 (C=O), 1450, 1295, 1150, 1128. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.55–0.95 (m, 9H, C_4H_9), 1.83 (dd, $J_{5,8s}$ = 1.2 Hz, $J_{8a,8s}$ = 14.9 Hz, 1H, 8-H_s), 2.61 (m, 1H, 6-H), 2.74–2.84 (m, 3H, 4-, 5-H, 8-H_a), 3.16 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.58 (d, $J_{1,6}$ = 1.0 Hz, 1H, 1-H), 3.77 (d, J_{AB} = 14.2 Hz, 1H, NCH), 5.18 (d, J_{AB} = 14.2 Hz, 1H, NCH), 7.23–7.88 (m, 10H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 13.7, 22.2, 28.9, 29.1 (C_4H_9), 32.8 (C-8), 34.3 (C-6), 40.1 (C-4), 48.2 (OCH_3), 49.2 (OCH_3),

49.6 (NCH_2), 58.3 (C-5), 65.4 (C-1), 103.5 (C-7), 127.9, 128.4, 128.6, 129.4, 129.6, 134.0, 136.7, 138.5 ($C_{arom.}$), 171.0 (C-3).

$C_{26}H_{33}NO_5S$ (471.6)
Calcd. C 66.22 H 7.05 N 2.97
Found C 66.20 H 6.97 N 2.84

(±)-(6-syn)-2-Benzyl-7,7-dimethoxy-6-methyl-2-azabicyclo[2.2.2]octan-3-one (**4a**): Compound **2a** (1.0 g, 2.3 mmol) was dissolved in warm methanol (80 ml), and sodium dihydrogen phosphate (2.0 g) was added. To the stirred suspension was added sodium amalgam (6.0 g, 9.4 mmol Na) in six portions. The mixture was stirred until all starting material was consumed [TLC, $CHCl_3$/MeOH (9 + 1); 24 – 36 h]. Separation of the mercury and evaporation of the solvent provided an oily residue which was dissolved in dichloromethane and washed with satd. ammonium chloride solution and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated. The remaining oil was triturated with petroleum ether to give colorless crystals; yield 0.56 g (97%), m.p. 93°C. – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1650 (C=O), 1462, 1450, 1122, 1040. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.49 (d, J = 7.0 Hz, 3H, CH_3), 1.15 (dd, $J_{5,6}$ = 5.3 Hz, J_{AB} = 13.1 Hz, 1H, 5-H), 1.63 (dd, $J_{4,8a}$ = 2.4 Hz, J_{AB} = 13.7 Hz, 1H, 8-H_a), 1.86 (d, J_{AB} = 13.1 Hz, 1H, 5-H), 2.00 (d, J_{AB} = 13.7 Hz, 1H, 8-H_s), 2.16 (m, 1H, 6-H), 2.61 (m, 1H, 4-H), 3.04 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 3.30 (d, $J_{1,6}$ = 1.5 Hz, 1H, 1-H), 4.09 (d, J_{AB} = 14.4 Hz, 1H, NCH), 4.95 (d, J_{AB} = 14.4 Hz, 1H, NCH), 7.29 – 7.34 (m, 5H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 19.5 (CH_3), 26.6 (C-5), 31.7 (C-8), 34.9 (C-6), 39.0 (C-4), 47.9 (OCH_3), 49.1 (OCH_3), 50.2 (NCH_2), 62.5 (C-1), 104.2 (C-7), 127.4, 128.3, 129.5, 137.5 ($C_{arom.}$), 174.3 (C-3). – MS (70 eV): *m/z* (%) = 289 (12) [M^+], 242 (7) [$M^+ - OCH_3 - CH_3$], 199 (47) [M^+ – Bzl], 173 (24), 158 (19), 91 (100).

$C_{17}H_{23}NO_3$ (289.4)
Calcd. C 70.56 H 8.01 N 4.84
Found C 70.78 H 8.16 N 4.88

(±)-(6-syn)-2-Benzyl-6-ethyl-7,7-dimethoxy-2-azabicyclo[2.2.2]octan-3-one (**4b**): Prepared in the same manner as described for **4a** from **2b** (1.0 g, 2.25 mmol); yield 0.62 g (91%), m.p. 146°C. – Starting from **5b**[1b)] (1.0 g, 1.7 mmol) the yield was 0.51 g (98%). – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 2930, 1650 (C=O), 1462, 1450, 1445, 1128. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.50 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.80 (m, 2H, CH_2CH_3), 2.21 (m, 1H, 5-H), 1.63 (dd, $J_{4,8a}$ = 2.4 Hz, J_{AB} = 13.7 Hz, 1H, 8-H_a), 1.87 (m, 2H, 5-H, 6-H), 2.04 (d, J_{AB} = 13.7 Hz, 1H, 8-H_s), 2.61 (m, 1H, 4-H), 3.06 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 3.42 (s, 1H, 1-H), 4.03 (d, J_{AB} = 14.3 Hz, 1H, NCH), 5.01 (d, J_{AB} = 14.3 Hz, 1H, NCH), 7.23 – 7.35 (m, 5H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_2CH_3), 26.7 (CH_2CH_3), 30.52 (C-5), 34.1 (C-8), 35.0 (C-6), 39.0 (C-4), 47.9 (OCH_3), 48.9 (OCH_3), 50.0 (NCH_2), 59.7 (C-1), 104.3 (C-7), 127.5, 128.3, 129.6, 137.4 ($C_{arom.}$), 174.6 (C-3). – MS (70 eV): *m/z* (%) = 303 (13) [M^+], 272 (6) [$M^+ - OCH_3 - CH_3$], 213 (59) [M^+ – Bzl], 187 (18), 158 (29), 91 (100).

$C_{18}H_{25}NO_3$ (303.4)
Calcd. C 71.26 H 8.31 N 4.62
Found C 71.47 H 8.51 N 4.64

(±)-(6-syn)-2-Benzyl-7,7-dimethoxy-6-vinyl-2-azabicyclo[2.2.2]octan-3-one (**4c**): Prepared in the same manner as described for **4a** from **2c** (0.18 g, 0.41 mmol); yield 0.11 g (89%), m.p. 63 – 65°C. – IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1}, 2840, 1655 (C=O), 1465, 1455, 1423, 1132. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.53 (m, 1H, 5-H), 1.70 (dd, $J_{4,8a}$ = 2.5 Hz, J_{AB} = 13.8 Hz, 1H, 8-H), 1.89 (m, 1H, 5-H), 2.01 (m, J_{AB} = 13.8 Hz, 1H, 8-H), 2.70 (m, 2H, 4-, 6-H), 2.98 (s, 3H, OCH_3), 3.17 (s, 3H, OCH_3), 3.41 (d, $J_{1,6}$ = 1.6 Hz, 1H, 1-H), 4.19 (d, J_{AB} = 14.5 Hz, 1H, NCH), 4.81 (d, J_{AB} = 14.5 Hz, 1H, NCH), 4.69 (m, 1H, $H_{olef.}$), 4.93 (m, 1H, $H_{olef.}$), 5.16 (m, 1H, $H_{olef.}$), 7.24 – 7.31 (m, 5H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 29.4 (C-5), 35.1 (C-8), 37.1 (C-6), 39.0 (C-4), 47.9 (OCH_3), 49.1 (OCH_3), 50.2 (NCH_2), 62.17 (C-1), 103.7 (C-7), 114.8 ($CH=CH_2$), 127.4, 128.3, 129.5, 137.3 ($C_{arom.}$), 139.9 ($CH=CH_2$), 174.4 (C-3).

$C_{18}H_{23}NO_3$ (301.4)
Calcd. C 71.74 H 7.69 N 4.65
Found C 71.75 H 7.66 N 4.55

(±)-(6-syn)-2-Benzyl-7,7-dimethoxy-6-methyl-2-azabicyclo[2.2.2]octane (**6a**): Compound **4a** (1.0 g, 3.5 mmol) was dissolved in THF (60 ml), cooled to 0°C. After addition of $LiAlH_4$ (0.19 g, 5 mmol) the mixture was stirred for ca. 12 h. The mixture was hydrolyzed with 2 N NaOH and extracted with dichloromethane (5 ×). The combined organic phases were washed with water, dried (Na_2SO_4), and the solvent was evaporated. The remaining colorless oil solidified at –20°C to a waxy solid; yield 0.92 g (98%), m.p. 43°C. – IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1}, 2865, 1452, 1365, 1155, 1122, 1042. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.96 (m, 1H, 6-H), 1.12 (d, J = 6.8 Hz, 3H, CH_3), 1.53 – 2.05 (m, 4H), 2.26 (m, 1H), 2.51 (s, 1H, 1-H), 2.80 (m, 1H, 3-H), 3.17 (s, 3H, OCH_3), 3.20 (m, 1H, 3-H), 3.25 (s, 3H, OCH_3), 3.78 (d, J_{AB} = 13.8 Hz, 1H, NCH), 3.91 (d, J_{AB} = 13.8 Hz, 1H, NCH), 7.17 – 7.40 (m, 5H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 20.0 (CH_3), 28.2, 28.8, 33.2 (C-8), 36.9 (C-4), 47.6 (OCH_3), 47.9 (OCH_3), 54.5 (NCH_2), 60.5 (C-3), 62.5 (C-1), 104.5 (C-7), 126.4, 127.9, 128.5, 141.2 ($C_{arom.}$). – MS (70 eV): *m/z* (%) = 275 (12) [M^+], 260 (46) [$M^+ - CH_3$], 244 (9) [$M^+ - OCH_3$], 200 (9), 169 (13), 91 (100).

$C_{17}H_{25}NO_2$ (275.4)
Calcd. C 74.14 H 9.15 N 5.09
Found C 73.99 H 9.14 N 5.04

(±)-(6-syn)-2-Benzyl-6-ethyl-7,7-dimethoxy-2-azabicyclo[2.2.2]octane (**6b**): Prepared in the same manner as described for **6a** from **4b** (1.0 g, 3.3 mmol); yield 0.92 g (96%), m.p. 25 – 28°C. – IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1}, 2860, 1452, 1362, 1145, 1105, 1042. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.3 Hz, 3H, CH_2CH_3), 0.99 (m, 1H, CH_2CH_3), 1.31 (m, 1H, CH_2CH_3), 1.50 – 1.85 (m, 5H), 2.26 (m, 1H), 2.64 (s, 1H, 1-H), 2.81 (ddd, J = 2.3 Hz, 3.6 Hz, 8.7 Hz), 3.15 (s, 3h, OCH_3), 3.20 (m, 1H), 3.25 (s, 3H, OCH_3), 3.76 (d, J_{AB} = 13.6 Hz, 1H, NCH), 3.90 (d, J_{AB} = 13.6 Hz, 1H, NCH), 7.19 – 7.37 (m, 5H, $H_{arom.}$). – ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_2CH_3), 27.2 (CH_2CH_3), 28.1, 31.8, 36.3 (C-8), 31.7 (C-4), 47.5 (OCH_3), 47.9 (OCH_3), 54.6 (NCH_2), 57.7 (C – 3), 62.4 (C-1), 104.5 (C-7), 126.4, 127.9, 128.5, 141.2 ($C_{arom.}$). – MS (70 eV): *m/z* (%) = 289 (11) [M^+], 274 (37) [$M^+ - CH_3$], 258 (8) [$M^+ - OCH_3$], 200 (33), 91 (100).

$C_{18}H_{27}NO_2$ (289.4)
Calcd. C 74.7 H 9.40 N 4.84
Found C 74.38 H 9.58 N 4.70

(±)-(6-syn)-7,7-Dimethoxy-6-methyl-2-azabicyclo[2.2.2]octane (**7a**): A solution of **6a** (1.0 g, 3.6 mmol) in methanol (50 ml) was hydrogenated over 10% Pd/C (0.15 g) at 2 bar for 5 h. After filtration and evaporation of the solvent the oily residue was distilled in a Büchi kugelrohr at 60°C/10^{-3} mbar; yield 0.65 g (97%). – IR (film): $\tilde{\nu}$ = 3370 cm^{-1} (NH), 2930, 2860, 1450, 1432, 1128, 1045. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.03 (m, 1H, 6-H), 1.12 (d, J = 7.0 Hz, 3H, CH_3), 1.61 – 1.81 (m, 4H, 5-, 8-H), 1.95 (br. s, 1H, NH), 2.08 (m, 1H, 4-H), 2.58 (d, $J_{1,6}$ = 1.9 Hz, 1H, 1-H), 2.80 (s, 2H, 3-H), 3.18 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3). – ^{13}C NMR ($CDCl_3$): δ = 20.1 (CH_3), 26.5, 27.5, 33.4 (C-8), 36.8 (C-4), 46.4 (C-3), 48.1 (OCH_3), 48.2 (OCH_3), 53.5 (C-1), 102.5 (C-7). – MS (70 eV): *m/z*

(%) = 185 (34) $[M^+]$, 170 (73) $[M^+ - CH_3]$, 154 (30) $[M^+ - OCH_3]$, 138 (74), 95 (100).

$C_{10}H_{19}NO_2$ (185.3)
Calcd. C 64.83 H 10.34 N 7.56
Found C 64.55 H 10.08 N 7.63

(±)-(6-syn)-6-Ethyl-7,7-dimethoxy-2-azabicyclo[2.2.2]octane (**7b**): Prepared in the same manner as described for **7a**; yield 0.65 g (94%) of a colorless oil. – IR (film): ṽ = 3370 cm^{-1} (NH), 2955, 2935, 1455, 1128, 1050. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.06 (m, 1H, CH_2CH_3), 1.43 – 1.81 (m, 7H, CH_2CH_3, 4-, 5-, 6-, 8-H), 2.09 (br. s, 1H, NH), 2.72 (d, $J_{1,6}$ = 1.2 Hz, 1H, 1-H), 2.79 (d, *J* = 1.9 Hz, 2H, 3-H), 3.18 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3). – ^{13}C NMR ($CDCl_3$): δ = 11.9 (CH_2CH_3), 27.3, 27.5, 31.9, 33.9, 37.1 (C-4), 46.4 (C-3), 48.0 (OCH_3), 48.2 (OCH_3), 51.4 (C-1), 102.4 (C-7). – MS (70 eV): *m/z* (%) = 199 (36) $[M^+]$, 184 (88) $[M^+ - CH_3]$, 168 (31) $[M^+ - OCH_3]$, 152 (72) $[M^+ - OCH_3 - CH_3]$, 109 (100).

$C_{11}H_{21}NO_2$ (199.3)
Calcd. C 66.30 H 10.62 N 7.02
Found C 66.18 H 10.73 N 7.14

(±)-(6-syn)-2-[2-(3-Indolyl)-1-oxoethyl]-7,7-dimethoxy-6-methyl-2-azabicyclo[2.2.2]octane (**9a**): Compounds **7a** (0.47 g, 2.5 mmol) and **8** (0.66 g, 3.75 mmol) were dissolved under nitrogen in dichloromethane and cooled to –20°C. After the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.4 g, 7.5 mmol) the mixture was stirred at –20°C for 1 h. Then diluted hydrochloric acid was added, and the separated organic phase was washed with $NaHCO_3$ solution and water. After drying (Na_2SO_4) and evaporation of the solvent, the oily residue was dissolved in $CHCl_3$/ethyl acetate (9 + 1) and chromatographed over neutral aluminium oxide. After evaporationof the solvent the remaining oil was crystallized with diisopropyl ether; yield 0.55 g (64%) of a colorless powder, m.p. 108°C. – IR (KBr): ṽ = 3220 cm^{-1} (NH), 2960, 1635 (C=O), 1435, 1131, 1040. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (m, 1H, 6-H), 0.95 (d, *J* = 7.0 Hz, 3H, CH_3), 1.55 – 1.99 (m, 4H, 5-, 8-H), 2.23 (m, 1H, 4-H), 3.17 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 3.40 (s, 2H, 3-H), 3.77 (d, *J* = 1 Hz, 2H, CH_2CON), 4.53 (d, $J_{1,6}$ = 1.6 Hz, 1H, 1-H), 7.05 – 7.61 (m, 5H, $H_{arom.}$), 8.51 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 20.0 (CH_3), 27.0, 27.8, 30.8, 33.1, 36.5, 48.0 (OCH_3), 48.9 (OCH_3), 49.2 (C-3), 51.0 (C-1), 102.1 (C-7), 108.8, 111.2, 118.5, 119.2, 121.8, 122.8, 127.4, 136.2 ($C_{arom.}$), 171.7 (C=O). – MS (70 eV): *m/z* (%) = 342 (15) $[M^+]$, 310 (20) $[M^+ - OCH_3]$, 170 (42), 130 (100%).

$C_{20}H_{26}N_2O_3$ (342.4)
Calcd. C 70.15 H 7.65 N 8.18
Found C 70.45 H 7.83 N 8.15

(±)-(6-syn)-6-Ethyl-2-[2-(3-indolyl)-1-oxoethyl]-7,7-dimethoxy-2-azabicyclo[2.2.2]octane (**9b**): Prepared in the same manner as described for **9a** from **7b** (1.01 g, 5.0 mmol) and **8** (1.3 g, 7.5 mmol) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.8 g, 15.0 mmol); yield 1.6 g (90%) crude material (TLC), 0.85 g (48%) pure product, m.p. 119°C (diisopropyl ether) (ref.$^{4e)}$: colorless oil). – IR (KBr): ṽ = 3215 cm^{-1} (NH), 2930, 1625 (C=O), 1430, 1268, 1042. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.25 (m, 2H, CH_2CH_3), 1.57 – 2.01 (m, 6H, 4-, 5-, 6-, 8-H), 3.16 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 3.39 (s, 2H, CH_2CON), 3.76 (s, 2H, 3-H), 4.65 (d, $J_{1,6}$ = 1.4 Hz, 1-H), 7.06 – 7.60 (m, 5H, $H_{arom.}$), 8.45 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_2CH_3), 27.6, 27.7, 30.7, 31.7, 34.5, 36.8, 48.0, 48.8, 49.1, 49.3, 102.1, 109.0, 111.1, 118.6, 119.3, 122.8, 123.2, 127.4, 136.2, 171.5 (C=O). – MS (70 eV): *m/z* (%) = 356 (65) $[M^+]$, 324 (11) $[M^+ - OCH_3]$, 184 (21), 130 (100).

$C_{21}H_{28}N_2O_4$ (356.4)
Calcd. C 70.76 H 7.92 N 7.86
Found C 70.41 H 7.92 N 7.57

(±)-21-Nor-7-oxo-18-(tosyloxy)ibogamine (**10a**): To a solution of anhydrous *p*-toluenesulfonic acid (0.304 g, 1.76 mmol) in benzene (60 ml) **9a** (0.30 g, 0.88 mmol) was added. The solvent was slowly distilled off (30 min) and the residue dissolved in dichloromethane. The organic phase was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the solvent evaported. The residue was crystallized from ether/methanol; yield 0.32 g (81%) colorless crystals, m.p. 175 – 177°C. – IR (KBr): ṽ = 3175 cm^{-1} (NH), 2940, 1615 (C=O), 1315, 1288, 1272. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 8.2 Hz, 3H, CH_3), 1.62 (m, 1H), 1.84 (m, 1H), 2.10 (s, 3H, toluene CH_3), 2.18 (m, 1H), 2.37 – 2.66 (m, 3H), 3.27 (d, J_{AB} = 19.7 Hz, 1H), 3.48 (m, 2H), 3.60 (d, J_{AB} = 19.7 Hz, 1H), 4.04 (s, 1H), 6.60 – 7.73 (m, 8H, $H_{arom.}$), 8.12 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, toluene CH_3), 22.8 (q, C-20), 29.9 (t, C-1), 31.7 (d), 31.8 (d), 32.5 (t), 34.8 (t), 50.8 (t, C-19), 63.6 (s, C-18), 86.9 (d, C-5), 106.0 (s, C-9), 111.3 (d), 113.2 (d), 119.9 (d), 122.5 (d), 125.3 (s), 127.1 (d), 129.1 (d), 131.3 (s), 132.3 (s, $C_{arom.}$), 136.5 (s), 144.8 (s, C-17), 169.9 (s, C-7). – MS (70 eV): *m/z* (%) = 278 (64) $[M^+ - \text{tosyloxy}]$, 223 (52), 172 (59), 91 (100).

$C_{25}H_{26}N_2O_4S$ (450.6)
Calcd. C 66.65 H 5.82 N 6.22
Found C 66.37 H 5.86 N 6.32

(±)-7-Oxo-18-(tosyloxy)ibogamine (**10b**): Prepared in the same manner as described for **10a** with 0.145 g (0.84 mmol) *p*-toluenesulfonic acid and **9b** (0.15 g, 0.42 mmol) in benzene (30 ml); yield 0.15 g (77%) colorless crystals, m.p. 148 – 150°C (ref.$^{4d)}$: amorphous, ref.$^{4e)}$: 140 – 145°C). – IR (KBr): ṽ = 3270 cm^{-1} (NH), 2955, 1618 (C=O), 1408, 1352, 1170. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.0 (t, *J* = 7.3 Hz, 3H), 1.41 – 1.95 (m, 5H), 2.11 (s, 3H, toluene CH_3), 2.26 (m, 1H), 2.46 (m, 1H), 2.61 (m, 1H), 3.28 (d, J_{AB} = 19.6 Hz, 1H), 3.49 (m, 2H), 3.59 (d, J_{AB} = 19.6 Hz, 1H), 4.14 (s, 1H), 6.16 – 7.31 (m, 8H, $H_{arom.}$), 8.26 (s, 1H, NH) [correspond with data described in ref.$^{4e)}$]. – ^{13}C NMR ($CDCl_3$): δ = 13.1, 21.4, 29.0, 29.7, 29.9, 31.8, 35.4, 39.0, 50.7, 63.4, 85.8, 106.0, 111.4, 114.7, 118.2, 119.9, 122.5, 125.4, 127.2, 129.1, 131.5, 132.5, 136.6, 144.7, 168.9. – MS (70 eV): *m/z* (%) = 292 (56) $[M^+ - \text{Tosyloxy}]$, 263 (22), 223 (100), 195 (50) [correspond with data in ref.$^{4e)}$].

$C_{26}H_{28}N_2O_4S$ (464.6)
Calcd. C 67.22 H 6.07 N 6.03
Found C 67.52 H 6.12 N 6.17

(±)-21-Noribogamine (**11a**): To a solution of anhydrous aluminium chloride (2.06 g, 15.5 mmol) in THF (40 ml) was added $LiAlH_4$ (0.58 g, 15.5 mmol), and the mixture was stirred for 10 min$^{3c)}$. To this mixture a solution of **10a** (0.2 g, 0.44 mmol) in THF (10 ml) was added and stirring was continued for 3 h. After the addition of 2 N NaOH the mixture was extracted with dichloromethane (4 ×), the combined organic extracts were washed with water, dried (Na_2SO_4), and the solvent was evaporated. The yellow oily residue was dissolved in $CHCl_3$/ethyl acetate (9 + 1) and "filtrated" over neutral aluminium oxide. After evaporation of the solvent the remaining colorless oil was crystallized from *n*-hexane; yield 0.06 g (51%) colorless crystals, m.p. 155 – 156°C. – IR (KBr): ṽ = 3390 cm^{-1} (NH), 2910, 2850, 1460, 1360. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 5.7 Hz, 3H, CH_3), 1.19 (m, 1H), 1.62 (m, 1H), 1.83 (m, 3H), 2.02 (m, 1H), 2.72 (m, 2H), 2.92 – 3.49 (m, 6H), 7.04 – 7.49 (m, 4H, $H_{arom.}$), 7.63 (s, 1H, NH). – ^{13}C NMR

($CDCl_3$): δ = 20.6 (q, C-20), 20.7 (t, C-8), 26.6 (d, C-2), 33.5 (t, C-3), 33.8 (t, C-1), 34.2 (d, C-4), 41.5 (d, C-18), 49.8 (t, C-7), 54.1 (t, C-19), 60.0 (d, C-5), 109.2 (s, C-9), 110.0 (d, C-14), 117.9 (d, C-11), 119.0 (d, C-12), 120.9 (d, C-13), 129.7 (s, C-10), 134.6 (s, C-15), 141.7 (s, C-17). – MS (70 eV): *m/z* (%) = 266 (61) [M^+], 195 (31), 180 (5), 168 (11), 156 (19), 135 (32), 122 (100).

$C_{18}H_{22}N_2$ (266.4)
Calcd. C 81.16 H 8.32 N 10.52
Found C 80.57 H 8.17 N 10.77

(±)-Ibogamine (**11b**): Prepared in the same manner as described for **11a** with anhydrous aluminum chloride (2.33 g, 17.5 mmol) in THF (50 ml), $LiAlH_4$ (0.68 g, 17.5 mmol) and **10b** (0.23 g, 0.5 mmol); yield 0.07 g (51%) colorless crystals, m.p. 129–132°C (ref.[4d]: 127–128°C) (ref.[4e]: 130–132°C). – IR (KBr): $\tilde{\nu}$ = 3395 cm^{-1} (NH), 2905, 2845, 1465, 1355. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.9 Hz, 3H, CH_3), 1.17–2.11 (m, 8H), 7.04–7.49 (m, 4H, $H_{arom.}$), 7.70 (s, 1, NH) [correspond with data in ref.[4e]]. – ^{13}C NMR ($CDCl_3$): δ = 11.9 (C-21), 20.5 (C-8), 26.3 (C-2), 27.7 (C-20), 31.9 (C-3), 34.0 (C-1), 41.1 (C-18), 41.8 (C-4), 49.9 (C-7), 54.2 (C-19), 57.7 (C-5), 109.0 (C-9), 110.1 (C-14), 117.9 (C-11), 119.1 (C-12), 121.0 (C-13), 129.6 (C-10), 134.6 (C-15), 141.5 (C-17) [correspond with data in ref.[10a]]. – MS (70 eV): *m/z* (%) = 280 (69) [M^+], 265 (17) [$M^+ - CH_3$], 251 (3), 195 (36), 180 (7), 156 (21), 149 (36), 140 (12), 136 (100), 135 (62), 124 (13), 122 (37).

$C_{19}H_{24}N_2$ (280.4)
Calcd. C 81.38 H 8.63 N 9.99
Found C 80.70 H 8.79 N 10.03

CAS Registry Numbers

2a: 129217-49-8 / 5-*anti*,6-*syn*-**2b**: 129217-50-1 / 5-*syn*,6-*syn*-**2b**: 129263-24-7 / **2c**: 129217-51-2 / **2d**: 129217-52-3 / **3**: 121851-97-6 / **4a**: 129217-53-4 / **4b**: 129217-54-5 / **4c**: 129217-55-6 / **6a**: 129217-56-7 / **6b**: 129217-57-8 / **7a**: 129217-58-9 / **7b**: 129217-59-0 / **8**: 87-51-4 / **9a**: 129217-60-3 / **9b**: 81177-00-6 / **10a**: 129217-61-4 / **10b**: 26512-15-2 / **11a**: 129217-62-5 / **11b**: 2288-55-3

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